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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,176	SCHREIBER ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 24 March 2004.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) 5,7 and 14-22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4,6 and 8-13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 3/24/2004. Claims 1 and 10-13 have been amended, no claim has been canceled, and no claim has been added. Claims 1-4,6 and 8-13 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Priority

Acknowledgement of claim to foreign priority of European Application, 00114786.7, filed 7/10/2000 under 35 U.S.C. 119(a)-(d) has been made and the certified translation of the same has been received as of 3/24/2004, as such the priority is herein granted.

Response to Declaration

The Katz-type declaration filed under 37 CFR 1.132 filed 3/24/2004 is sufficient to overcome the rejection of claims 1-4, 6, and 8-13 based upon 35 U.S.C. 102(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-4, 6, and 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a non-responder to infliximab anti-TNF therapy for Crohn's disease, by testing an individual for homozygosity of the single nucleotide polymorphism(SNP) that is a nucleotide substitution A/G at position 168 from the transcription starting site in exon 2 of the gene coding for the TNF Receptor II, but does **not** reasonably provide enablement for;

- Detecting an individual's homozygosity for any, at least one SNP in the gene coding for the TNF Receptor II.
- Detecting a SNP in an individual who is a non-responder to any form of anti-TNF therapy.
- Detecting a SNP in an individual who is a non-responder to any form of anti-TNF therapy for any disease other than as a treatment for Crohn's.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-4, 6, and 8-13 are broadly drawn to a method of detecting non-responders to anti-TNF therapy, comprising testing an individual for homozygosity for at least one SNP in the gene coding for the TNF Receptor II. The claims are so broad as to encompass the method's execution with; any SNP located in the gene coding for the TNF Receptor, an individual who is not responding to any form of anti-TNF therapy, and lastly with an individual who may be receiving this Anti-TNF as treatment for any disease. However, as will be further discussed, there is no support in the specification and prior art for the methods as broadly as they are currently claimed. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites that homozygosity for the SNP in exon 6(Met →Arg @ amino acid position 196)(pg. 16), is "always associated with non-response to infliximab(i.e. neither reaching clinical improvement (drop of the Crohn's disease activity index(CDAI) by at least 70 points) nor remission (CDAI < 150 points) resulting in a test specificity of 100% in these individuals)"(Pg. 18 and table 4). The specification continues to assert that the "homozygote individuals show a marked reduction in clinical improvements after treatment with infliximab whereas a heterozygous genotype was not associated with a clinical response"(Pg. 18). On page 20 the specification teaches "a second mutation in the same gene, the silent mutation in exon 2(nucleotide substitution A/G at position 168), is in a high degree of linkage disequilibrium, i.e.

in almost complete linkage disequilibrium (4 discordant genotypes out of 90)...with the polymorphism in exon 6". The specification recites that specifically, homozygosity of the single nucleotide polymorphism(SNP) that is a nucleotide substitution A/G at position 168 from the transcription starting site in exon 2 of the gene coding for the TNF Receptor II, "although a silent mutation, can be used as a marker because it is in a high linkage disequilibrium with the mutation in exon 6"(Abstract). However, there is no teaching of any other SNP being in linkage disequilibria or being correlated to nonresponsive Crohn's patients to anti-TNF therapy. The specification further omits any teachings of results substantiating these previously defined roles of the exon 2 and 6 SNPS when any anti-TNF therapy, other than infliximab, is used. Lastly the specification is lacking any teachings concerning patients suffering from any disease other than Crohn's who are receiving the anti-TNF treatment.

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease

associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated. As a result, there is a great deal of unpredictability that exists in the invention without any guidance in the specification for example, to any polymorphism in the TNFR2 gene being correlated to anti-TNF therapy in the same way as are the disclosed SNPs in exons 2 and 6. Additional prior art corroborates this unpredictability in its teaching that "it is important to emphasize that all these associations between TNF2 allele and either phenotypes of CD[Crohn's disease] or TNFalpha production in inflamed mucosa are slight, borderline or even not statistically significant. This suggests that beside the TNF gene, other genetic or environmental factors are involved in the determination of these biological or clinical parameters"(Page 67 right, Clinical Exp. Immunol, 2000). Additionally, other factors are taught in the prior art as being unpredictable, such as the background and other loci's genetic makeup as is in the teaching that "although the linkage of CD to the MHC region has been repeatedly reported, considerable variations are present in the actual HLA-DRB1 alleles associated with CD among the populations"(Pg. 354 right, Genes and Immunity, 2000).

The post filing date art further confirms the unpredictability of this area. Shetty et al (Am J. Pharmacogenomics, 2002) teaches with respect to the unpredictability of extrapolating this data involving exons 2 and 6 to other diseases that "the findings of association studies and studies relating polymorphisms to TNF function have not been confidently reproduced elsewhere and some cases are conflicting"(Pg. 218, right). This reference also teaches the many different

routes to therapeutic inhibition of TNFalpha that are possible in their Table 1, and how each regiment varies in their mode of action. For example, "pentoxifylline affects the production of TNF by increasing intracellular cAMP concentration...clinical trials of pentoxifylline have, however, not confirmed any efficacy in Crohn's disease"(Pg. 219 left), let alone with the exon 2 and 6 polymorphisms. The reference also teaches that "thalidomide inhibits TNF by increasing the degradation of mRNA for TNF...to date there are no properly controlled trials"(Pg. 219). It is important to realize that infliximab's mode of action is through "neutralizing TNFalpha by blocking soluble cytokine"(Pg. 219, left), a mode that is quite different from the other anti-TNF therapies to which the action previously alluded. The complications involved with using any anti-TNF therapy to practice this method are highly unpredictable if not impossible because of the inherent differences in each therapy's mode of action. It is further unpredictable to use patients suffering from any disease or the use of any SNP in the TNF gene to practice this method as differences in the genetic background exists as alluded to in the prior art citation above, that make extrapolation of such correlations to all diseases quite unpredictable.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to the broadly claimed embodiments involving any SNP, any disease, and any anti-TNF therapy.
The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention as asserted by the specification, one would have to establish a relationship between the polymorphisms in exon 2 and in exon 6 with other SNPs in the same gene that are also associated with some other disease state, or some other anti-TNF therapy. In order to obtain the type of information necessary to practice the claimed invention,

one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in detecting nonresponders to anti-TNF treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the polymorphism and any disease or condition. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of the method using any SNP in the TNFR2 gene, to detect a non-responder to any anti-TNF therapy being used to treat a patient suffering from any disease.

Guidance in the Specification.

The specification provides no evidence that the disclosed method would be effective if practiced as broadly as it is claimed. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that if necessary other SNPs in the TNFR2 gene can be detected. Even if, arguendo, the detected SNPs in the TNFR2 gene are correlated with Crohn's disease, there is no support for a prophetic correlation to non-response to an anti-TNF therapy. There is no support for how such a correlation can be derived as only the

relationship between infliximab and the SNPs of exons 2 and 6 has been asserted by the specification.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the use of SNPs to detect disease states is even further unpredictable, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

Applicant's arguments filed 3/25/2004 have been fully considered but they are not persuasive. Applicant's assert that "the Examiner cites a number of relatively insignificant and sub-average studies" whose "improper selection of patients" or "insufficiently low number of patients" yielded data that cannot be compared with the applicant's "very restrictively' defined population. Furthermore, applicant asserts that "the relation between genetic and complex phenotype is considerably more complicated than expressed by the Examiner" and further that "the genetical state of the art by the Examiner is not complete". Applicant should also note that their arguments directed to the above deficiencies of the cited prior and post-filing date art are

not applicable as these limitations of patient selection, number of patients, population definition, statement of problem, and study design, are not in the claims and as a result are not the invention currently under prosecution. Applicant's claimed invention is a method for detecting non-responders to anti-TNF therapy with any TNF-binding protein by detecting any SNP in the gene coding for the TNF Receptor II. Applicant should also note that their introduction of the Hampe et al., Hugot et al., and Ogura et al. references cannot be relied upon for the enablement of their method as they are all post-filing date pieces of art. While applicant additionally assert that "genetic exploration yields predictable and reproducible results also in the case of complex disease" referencing Crohn's disease studies, correlations between any polymorphism and any disease remain unpredictable in the art. Applicant should note that the examiner's intent, in her provision of the prior and post-filing date art was to provide examples from different studies in which SNPs were attempting to be correlated with a disease state, not to exactly mimic the ideal study or applicant's own research guidelines. The state of the art section of the rejection provides only an overview and attempts to exemplify common problems had in the use of unpredictable methods. It is further asserted that the claiming of methods that correlate any SNP in the TNF Receptor II with the non-responding to any TNF-binding protein therapy for the treatment of any disease remains unpredictable as different SNPs have different effects within their environment and their effects cannot be generalized just because they are in the same gene. Furthermore it is important to note that many diseases have characteristically variant genetic backgrounds that could effect any given SNP in a different manner. As a result, applicants' assertion that "the phenomenon of non-response to anti-TNF-treatment is generic for anti-TNF-therapy of TNF-driven diseases, and therefore independent of a specific disease, and

theoretically also independent of the kind of TNF-binding protein" is not found to be convincing as the specification as original filed does not provide support for such a conclusion.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

6/10/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
6/9/04